REMARKS

Status of the claims

Claims 1-35 are currently pending. Claims 2-14 and 16-35 are directed to a non-elected invention, and are therefore cancelled. Applicants reserve the right to file a divisional on the non-elected subject matter. To emphasize the difference between the claimed amorphous celecoxib and crystalline celecoxib, claims 1 and 15 are amended to require that the amorphous celecoxib exhibits a glass transition measurable by differential scanning calorimetry. Support for this amendment may be found, for example, in Example 4 of the specification (page 29, lines 5-27).

New claims 36 and 37 have been added. Support for these claims may be found, for example, in Example 4 of the specification (page 29, lines 5-27) and Figures 4-6. No new matter has been added by this amendment.

Rejection of claims 1 and 15 under 35 U.S.C. §103(a)

Reconsideration is respectfully requested of the rejection of claims 1 and 15 under §103(a) as unpatentable over Talley et al., U.S. Patent No. 5,466,823, in view of Stavchansky & McGinity (1990) Bioavailability in Tablet Technology, ch. 6 in Pharmaceutical Dosage Forms: Tablets, Vol. 2, ed. Lieberman et al., pp. 349-569 ("Stavchansky").

Claim 1, as amended, is directed to amorphous celecoxib that exhibits a glass transition measurable by differential scanning calorimetry ("DSC"). Claim 15, as amended, is directed to a pharmaceutical composition comprising amorphous celecoxib, wherein the amorphous celecoxib exhibits a glass transition measurable by DSC.

Talley et al. describe substituted pyrazolyl benzenesulfonamides, including crystalline celecoxib (see Example 1c, col. 23, lines 11-14.

Stavchansky describes numerous factors that must be considered in the formulation and manufacture of drugs in the

tablet form, including:

> [t]he physical chemical properties of the drug, the characteristics of the dosage form in which the drug is administered, and the physiological factors controlling absorption, distribution, metabolism and elimination of the drug . . . .

See Stavchansky, page 353. Methods for improving bioavailability are described, including adjusting the particle size of the drug; using prodrugs; molecular dispersion considerations; polymorphism and crystal form; solvation and hydration; complexation; and consideration of drug-excipient interactions.

The Office asserts that Stavchansky teaches "that amorphous solids will, in general, be better absorbed than will crystalline ones (lines 11-12, page 463)." Applicants respectfully submit that the full quote from Stavchansky makes clear that this characteristic represents a mere prediction: "**[t]heoretical considerations predict** that amorphous solids will, in general, be better absorbed than will crystalline ones." Stavchansky, page 463, lines 11-12 (emphasis added). One skilled in the art would recognize that such a theoretical prediction cannot be read to imply that in all instances an amorphous solid will be better absorbed than a crystalline solid. Furthermore, formation of an amorphous solid is not always desirable, notwithstanding any benefits it may provide with respect to improved absorption. For instance, Stavchansky notes that "the amorphous state is predictably unstable," page 465 at line 7, and lists several examples of drugs that are either administered in crystalline form, or must be formulated with crystallization inhibitors, to avoid the stability problems of the amorphous form. Indeed, nowhere does Stavchansky describe or suggest that amorphous celecoxib may even be prepared and successfully formulated in a pharmaceutical composition, as claimed.

The Office also asserts that claims 1 and 15 are obvious in light of the statement in Stavchansky that "amorphous state

generally reduce [sic] the particle size of the drug and result in a faster rate of dissolution than occurs with a crystalline form (lines 5-7, page 465)." As previously noted by Applicants, the full quote from Stavchansky is that "**[t]echniques commonly used in preparing drugs** in the amorphous state generally reduce the particle size of the drug," see page 465, lines 4-6 (emphasis added), and neither claim 1 nor claim 15 are limited to amorphous celecoxib particles having a particular particle size. Furthermore, Stavchansky also teaches that "reduction in particle size is not desirable in all cases," see page 454, line 20, and thus the relevance of the above quote from Stavchansky is unclear.

Nothing in the Stavchansky reference, or in the art as a whole, would have motivated one skilled in the art to combine Talley et al.'s crystalline celecoxib with the teaching of Stavchansky to prepare the amorphous celecoxib of claims 1 and 15. This is particularly true when one considers Stavchansky as a whole, as required by MPEP 2141.02, because Stavchansky also teaches away from the amorphous form of drugs, as noted above. At the best, the Office appears to argue that preparation of the claimed amorphous celecoxib would have been "obvious to try" in view of Stavchansky. This is, of course, an improper standard, In re O'Farrell, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988); MPEP 2145. Furthermore, Stavchansky makes numerous suggestions for improving the bioavailability of a drug, but does not place any particular significance on preparing an amorphous form of a drug, and, in fact, describes several instances where such an approach would be unfavorable. Indeed, nothing in Stavchansky would have led one skilled in the art to have a reasonable expectation that preparing an amorphous form of celecoxib would provide a drug with better bioavailability and lacking any stability problems.

Furthermore, even assuming *arguendo* that one skilled in the art would have been motivated to combine the teaching of Talley et al. with that of Stavchansky to prepare an amorphous

celecoxib, a skilled artisan would have had no reasonable expectation of the success of such a combination. First, as one skilled in the art would know, there is no guarantee that a particular compound will form an amorphous solid:

> Certain materials are easy to cast into a glassy [i.e., amorphous] state, others can be made glassy with some difficulty and, some, seemingly not at all. At present there seems to be no specific theory to help predict this behavior.
> Remington, The Science and Practice of Pharmacy, p. 168 (19th ed., 1995).

Second, as noted above and as taught by Stavchansky, the physicochemical and pharmacokinetics properties of amorphous compounds are unpredictable, particularly compared to their crystalline counterparts. One skilled in the art could have no reasonable expectation of success in preparing the claimed amorphous celecoxib having a glass transition, and of successfully formulating the amorphous celecoxib in a pharmaceutical composition.

Applicants submit that claims 1 and 15 are patentable over the cited art and the art as a whole, and respectfully solicit allowance of all pending claims.

Notice of Appeal

A Notice of Appeal from the Examiner to the Board of Patent Appeals and Interferences is enclosed herewith.

Respectfully submitted,

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